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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,157	03/28/2006	Herman Augustinus De Kock	TIP005 1US/PCT	7766

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EXAMINER	
FIERRO, ALICIA	
ART UNIT	PAPER NUMBER
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,157	DE KOCK ET AL.	
	Examiner	Art Unit	
	Alicia L. Fierro	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/30/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 21-35 are pending in the instant application, according to the amended Listing of the Claims filed July 30, 2009.

Priority

2. The instant application is a national stage entry of PCT/EP2004/52382, filed September 30, 2004, which claims priority from U.S. Provisional Application No. 60/507,996, filed October 2, 2003 and European Patent Application No. 03103630.4, filed September 30, 2003. In view of the claim amendments cancelling the terms "prodrugs" and "metabolites" from the scope of the claims, the effective filing date of the claims is October 2, 2003.

Information Disclosure Statement

3. No Information Disclosure Statement has been filed in the instant application. Applicants are reminded of their duty to disclose all information known to them to be material to patentability as defined in 37 C.F.R. 1.56.

Maintained Specification Objections

4. The Examiner requests that the phrase "such a sarginine" in lines 3-4 on page 37 of the specification be changed to "such as arginine" to correct the typing error.

New Claim Rejections – 35 USC § 112

(second paragraph)

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 21-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to compounds and a method of preparing said compounds,; however, the claims are also drawn to "racemic mixtures thereof." Thus, it is unclear whether Applicant is intending the claim the compound and method of making said compound, or a composition of said compound and method of making said composition. For purposes of prosecution on the merits, the Examiner will interpret the claim as being drawn to the compound rather than a composition.

7. Claim 28 recites the limitation "R2 can be C1-6alkyl and R3 is C3-7cycloalkyl, phenyl, or C1-6alkyl" in the definitions of the respective variables. There is insufficient antecedent basis for this limitation in the independent claim 21, which requires that R2 is hydrogen and R3 is phenylmethyl.

8. Claim 32 recites the limitation "R3 is phenylC1-4alkyl". There is insufficient antecedent basis for this limitation in the independent claim 21, which requires that R3 is phenylmethyl.

New Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

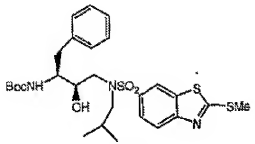
10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 31-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 2002/083657 A2 (Surleraux, et al.; publication date October 24, 2002) in view of Patani et al., *Chem Rev.*, 1996, 96, 3147-76.

12. The claims are drawn to compounds of formula (6), which is a benzoxazole sulfonamide compound useful as disclosed in the production of an HIV protease inhibitor, as well as methods

for their preparation. Scheme I on page 43 of the '657 publication discloses compound (i-4), which is a compound of instant formula (6), and also details its synthesis. The compound has the following structure:



(i-4)

13. The above compound corresponds to a compound of instant formula (6) wherein PG is Boc, R2 is H, R3 is phenylmethyl, R4 is isobutyl, E is CH_3, and the sulfonamide group is attached to the benzoxazole ring at the 6 position. Compound (i-4) is the exact compound of claim 34, for which claims 31-33 are generic, with the only difference being that the benzothiazole ring in the prior art is a benzoxazole ring in the instant application, which results in the change of the S in the ring to an O.

14. To those skilled in the chemical art, compounds are not patentably distinct when the claimed compounds and prior art compounds have a difference of one chalcogen vs. another chalcogen. Since both O and S are chalcogens, the claimed compounds are analogues or isologues of those in the '657 publication, which would be expected to behave similarly in chemical reactions because of their similar electronic properties. *Ex parte Wiseman*, 98 USPQ 277 (1953). Additionally, the instantly claimed compounds and that of the prior art are bioisosteres of one another. Patani et al. teaches that "bioisosterism represents one approach used by the medicinal chemist for the rational modification of lead compounds into safer and

more clinically effective agents," and further that the concept of bioisosterism is "intuitive" (page 3147, Introduction, column 1-column 2). Bioisosteric substitutions are well-known in the art. For example, O and S are isosteric (See Table 25, page 3158, compounds 52a and 52d). Case law has determined that when chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made. See for example *In re Wilder,* 563 F.2d 457, 195 USPQ 426 (CCPA 1977) (adjacent homologues and structural isomers); *In re May,* 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (steroisomers); In re *Hoch,* 428 F.2d 1341, 166 USPQ 406 (CCPA 1970) (acid and ethyl ester). When such "close" structural similarity to prior art compounds is shown, in accordance with these precedents the burden of coming forward shifts to the applicant, and evidence affirmatively supporting unobviousness is required.

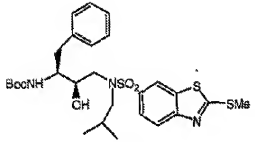
15. The instantly claimed compounds would have been *prima facie* obvious to one skilled in the art at the time the invention was made because one skilled in the art would have been motivated to prepare O vs. S bioisosteres of the compounds taught by the '657 publication with the expectation of obtaining compounds with similar properties and utilities (namely intermediates used to produce pharmacologically active HIV protease inhibitors). There would have been a reasonable expectation of success in producing compounds with similar properties since O and S are well-known bioisosteres which are taught in the prior art to produce chemically similar compounds.

16. Claims 21-24, 26, and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 2002/083657 A2 (Surleraux, et al.; publication date October 24, 2002) in view of

Patani et al., *Chem Rev*., 1996, 96, 3147-76, and further in view of Chu-Moyer et al., *J. Org. Chem*, 1995, 60 (17), 5721-5725.

17. The claims are drawn to a method for preparing a compound of formula (9) comprising aminating a compound of formula (6), deprotecting the resulting compound to arrive at a compound of formula (8), and coupling the compound of formula (8) with a radical R1-L to obtain the desired compound.

18. Scheme I on page 43 of the '657 publication discloses compound (i-4), which is a compound of instant formula (6), and also details its synthesis. The compound has the following structure:

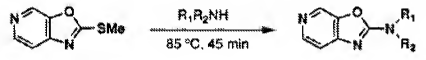


(i-4)

19. The above compound corresponds to a compound of instant formula (6) wherein PG is Boc, R2 is H, R3 is phenylmethyl, R4 is isobutyl, E is CH_3, and the sulfamide group is attached to the benzoxazole ring at the 6 position. Compound (i-4) is the exact compound as the starting material used in claim 21 (i.e. Compound 6), with the only difference being that the benzothiazole ring in the prior art is a benzoxazole ring in the instant application, which results in the change of the S in the ring to an O.

20. Regarding the process of making compound (9) beginning with compound (6), the '657 publication does not teach the amination of a compound of formula (6) as required by the first

step in claim 21. Rather, in the '657 publication compound (i-4) which corresponds to instant formula (6) is oxidized prior to amination, and compounds (i-6) and (i-5) are aminated. However, the amination of an S-alkyl group such as S-Me is a well known nucleophilic aromatic substitution reaction. Chu-Moyer et al. teach the following compounds and reactions:



3c 9a-f

entry	compd	$-NR_1R_2$	yield (%)
1	9a		96
2	9b		92
3[a]	9c		91
4	9d		90
5	9e		94
6	9f		88

21. One of ordinary skill in the art would have been motivated at the time the invention was made to alter the steps of the synthesis method by directly aminating the S-Me group rather than oxidizing it first, as is taught in Scheme I. The motivation to do so is based on the fact that the reaction shown about by Chu-Moyer et al. is a well-known synthesis method, which would allow for the elimination of an extra step in the method (namely the oxidation step). The '657 publication teaches that the amination step was carried out over a period of 20 hours and gave a 93% yield (page 44, lines 11 and 14), while the reaction taught by Chu-Moyer et al. was carried out for only 45 minutes, with no significant difference in yield of aminated product, as shown by

the table above. The amination step in the '657 publication yields a product which corresponds to instant formula (7) wherein R8 is hydrogen and R6 is ethylpyrrolidine (aminoC_{1-6}alkyl). Please note that because no definition of the term "amino" was given in the instant specification, the cyclic amino group (i.e. pyrrolidine) taught by the '657 publication is interpreted as reading on the broader term "amino."

22. Following the amination step, the '657 patent teaches the deprotection of compound (i-7) on page 44, lines 17-23, which forms a compound that corresponds with instant compound 8. Finally, compound (i-7) was reacted with 1-[[[[(3S,3aR,6aS)+(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl]oxy]carbonyl]oxy]-2,5-pyrrolidinedione, which had the effect of coupling a radical of instant formula R_1-L [where L is O-C(=O) and R1 is a bicyclic heterocycle having 8 ring members] to compound (i-7) to form compound 20. Compound 20 of the '657 publication corresponds to a compound of instant formula (9).

23. Additionally, Scheme I on page 43 teaches a method of making compound (i-4) from compound (i-1). Compound (i-1) corresponds to instant compound (2) wherein E is Me. Compound (i-1) is further sulfonated by ClSO3H to form compound (i-2), which corresponds to instant compound (3) wherein LG is Cl. Finally, compound (i-2) is reacted with compound (i-3) to form compound (i-4). Compound (i-3) corresponds to instant compound (5) as recited in instant claims 28-30, wherein R4 is isobutyl, R3 is phenylmethyl, R2 is H and PG is Boc. The '657 publication also details the synthesis of a compound (f-2) which is a species of the genus encompassed by formula (5), wherein PG is Boc, R3 is phenylmethyl, and R4 is methylpyridine from the compound 2S,3S-1,2-epoxy-3-(*tert*-butoxycarbonylamino)-4-phenylbutane which is a compound of instant formula (4) as in claim 30 wherein R3 is methylphenyl and PG is Boc.

Although the reference is silent as to the methods of preparation of compound (i-1), in the instant case where E is CH_3 the interchange of H and CH3 is obvious. Hydrogen and methyl substitutions are known in the art and are deemed to be obvious variants of each other. *In re Wood*, 199 USPQ 137. Thus, the step of alkylating the mercapto group by adding a methyl group is an obvious variation of the known method.

24. To those skilled in the chemical art, compounds are not patentably distinct when the claimed compounds and prior art compounds have a difference of one chalcogen vs. another chalcogen. Since both O and S are chalcogens, the claimed compounds are analogues or isologues of those in the '657 publication. *Ex parte Wiseman*, 98 USPQ 277 (1953). Additionally, the instantly claimed compounds and that of the prior art are bioisosteres of one another. Patani et al. teaches that "bioisosterism represents one approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents," and further that the concept of bioisosterism is "intuitive" (page 3147, Introduction, column 1-column 2). Bioisosteric substitutions are well-known in the art. For example, O and S are isosteric (See Table 25, page 3158, compounds 52a and 52d). Case law has determined that when chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made. See for example *In re Wilder,* 563 F.2d 457, 195 USPQ 426 (CCPA 1977) (adjacent homologues and structural isomers); *In re May,* 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (steroisomers); In re *Hoch,* 428 F.2d 1341, 166 USPQ 406 (CCPA 1970) (acid and ethyl ester). When such "close" structural similarity to prior art compounds is shown, in accordance with these precedents the burden of coming forward shifts to the applicant, and evidence affirmatively supporting unobviousness is required.

25. The instantly claimed compounds would have been *prima facie* obvious to one skilled in the art at the time the invention was made because one skilled in the art would have been motivated to prepare analogues or bioisosteres of the compounds taught by the '657 publication with the expectation of obtaining compounds with similar properties and utilities (namely intermediates used to produce pharmacologically active HIV protease inhibitors). Because the compounds would be *prima facie* obvious, as determined above, the methods of making as in claims 21-24, 26 and 28-30 would also be *prima facie* obvious, as the steps and the structures of the intermediates used to make compound (6) are all exactly the same as the prior art, with the only difference being the substitution of the sulfur in the prior art for an oxygen in the instant claims in the starting material. Regarding the steps involved in starting with compound (6) to produce a compound of formula (9), it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to combine the compounds and method taught by the '657 with the information on bioisosteres from Patani et al. to obtain compounds with similar activity, and to further combine this with the teachings on amination in Chu-Moyer et al. Chu-Moyer et al. shows that directly aminating an S-Me group is a known reaction which would allow for the synthesis of an aminated ring structure in less time than the method taught by the '657 publication while still obtaining a high yield of aminated product. This would have given *prima facie* obvious motivation to combine these three references with a reasonable expectation of success.

26. Claims 27 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 2002/083657 A2 (Surleraux, et al.; publication date October 24, 2002) in view of Patani et al.,

Chem Rev., 1996, 96, 3147-76, and Chu-Moyer et al., *J. Org. Chem*, 1995, 60 (17), 5721-5725 as applied to claims 21-24, 26, and 28-34 above, and further in view of Berge et al. *J. Pharm. Sci.*, 1977, 66 (1), 1-19.

27. Taken together, the above references do not teach the specific salt forms of compounds (6) and (9) claimed by Applicant. Berge et al. teaches the benefits of preparing salts of pharmaceutical compounds. The reference teaches that "salt formation is a means of altering the physical, chemical, and biological characteristics of a drug without modifying its chemical structure" and further that "the salt form can have a dramatic influence on the overall properties of the parent compound" (p. 16, Conclusions section). Although the reference discloses that, at the time it was written, there was not a way to knowingly predict how a particular salt would affect the properties of a given compound, it provides many factors and considerations which would have led one of ordinary skill in the art to choose a salt form that would meet the limitations of claims 27 and 35. For example, Berge et al. teaches that "knowledge that one salt form imparts greater water solubility, is less toxic, or slows dissolution rate" would be beneficial to formulators and that sometimes generalizations can be made in this regard (page 2, column 2, paragraph 2). These factors, in turn, affect the bioavailability and formulation characteristics of a drug (p. 5, column 1, last paragraph). Additionally, salt formation is one of the first approaches considered to increase a compound's solubility in water (p.7, column 1-2). For example, the reference teaches that salt combinations with dicarboxylic acids confer water solubility on a compound if one carboxylic group is left free (page 2, column 2, paragraph 2). In the instant case, fumarate is a dicarboxylic acid salt.

28. One of ordinary skill in the art would have been motivated at the time the invention was made to make pharmaceutical salts of the instant compounds, and specifically to utilize the claimed salts such as fumarate. Berge et al. teaches that it is desirable for pharmaceutical chemists to impart water solubility on a pharmaceutical compound by creating, for example, dicarboxylic acid salts such as fumarate which are known to confer water solubility on a compound. This would lead to *prima facie* obvious motivation to combine these references with a reasonable expectation of success.

29. Applicant argues with the rejections in view of the fact that the primary reference (i.e. the '657 publication) does not teach or suggest the substitution of oxygen for sulfur in the core of the claimed compounds and methods of making, and that this deficiency is not cured by any of the secondary references. Specifically, Applicants state that "it is not apparent that the substitution of a different atom in a reaction of the complexity claimed can be simply substituted successfully in the preparation of different compounds." This argument is not found to be persuasive. As explained in the rejections above, compounds are not considered to be patentably distinct when the claimed compounds and prior art compounds have a difference of one chalcogen vs. another chalcogen. *Ex parte Wiseman*, 98 USPQ 277 (1953). Since both O and S are chalcogens, they have similar electronic configurations (i.e. the valence is the same) and therefore the compounds would be expected to react similarly. In addition to the *prima facie* case of obviousness established by the fact that O and S have the same electronic configuration since they are both chalcogens, the compounds ultimately produced by the claimed method are bioisosteres of each

other. As explained in the rejections above, Patani et al. teach that the concept of bioisosterism is a common and "intuitive" approach used by medicinal chemists to rationally modify lead compounds into new compounds which are more clinically effective, albeit useful for the same purpose. Bioisosteric substitutions are well-known in the art, and specifically O and S are well-known isosteres of one another (See Patani Table 25, page 3158, compounds 52a and 52d). Case law has determined that when chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made. See for example *In re Wilder,* 563 F.2d 457, 195 USPQ 426 (CCPA 1977) (adjacent homologues and structural isomers); *In re May,* 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (steroisomers); In re *Hoch,* 428 F.2d 1341, 166 USPQ 406 (CCPA 1970) (acid and ethyl ester). When such "close" structural similarity to prior art compounds is shown, in accordance with these precedents the burden of coming forward shifts to the applicant, and evidence affirmatively supporting unobviousness is required.

30. Applicants have not supplied any objective evidence to support their case for unobviousness. Further, although Applicants suggest that the substitution of O for S cannot be "simply substituted" in a complex reaction, the position at which the substitution would take place is not the site of any of the steps of the claimed reaction or the reaction taught by the '657 publication. Rather, the steps of the reaction take place on the substituents of the core structure and a person of ordinary skill in the art would not expect this substitution to interfere with reactions occurring at other parts of the compound. In addition, based on the Patani reference and the knowledge of the similar electronic configurations, a core structure containing O or S would be expected to participate in chemical reactions similarly.

Conclusion

31. No claims are allowed

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alicia L. Fierro whose telephone number is (571)270-7683. The examiner can normally be reached on Monday - Thursday 6:00-4:30 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

10. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

/Alicia L. Fierro/
Examiner, Art Unit 1626

/REI-TSANG SHIAO /
Primary Examiner, Art Unit 1628